The claims remain rejected for indefiniteness and obviousness.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 48 was rejected as indefinite. The claim has been amended to clarify the position of the carbonyl group oxygen in the recited structure. Accordingly, the rejection can be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 35-51 remain rejected as unpatentable over Bachovchin et al., J. Biol. Chem. 265:4738, 1993 ("the Bachovchin JBC publication"). The rejection is traversed.

All the pending claims require, *inter alia*, mixtures of stereoisomers in which at least 96% of the carbon atoms bearing boron are of the L-configuration. The Examiner maintains that claims including this limitation are obvious in view of the Bachovchin JBC publication, even in light of the remarks and accompanying declaration submitted in Applicants' previous response. Applicants respectfully request reconsideration of the rejection in view of the following comments.

Regarding the Bachovchin JBC publication, the Examiner states (page 5, first full paragraph of the Office Action):

> The reference has described the means to obtain Ala-boroPro in 95% enantiomeric excess; if the compound has in fact been misidentified, that is of little consequence from a legal standpoint.

Applicants disagree for the following reasons.

The language in The Bachovchin JBC publication apparently forming the basis of the Examiner's position appears at page 3743 of the reference:

> Preparation of H-Ala-boroPro-pinacol. Boc-Ala-boroPro-pinacol was deblocked at 0 °C with 3.5 molar excess of 4 N HCl-Dioxane. Reaction was stirred at 0 °C for 15 minutes and at room temperature for one hour. Flash-evaporation yielded a white foam

> approximately 95% enriched in a one isomer (*sic*). Because this early fraction has more inhibitory power than the later fractions at equal concentrations, we presume that early fraction is enriched in the L-boroPro isomer. These fractions were collected, precipitated with hexane to an extremely hydroscopic white powder. Further characterisation of the isomers based on stereospecific synthesis will be published in a separate paper.

The Examiner is in effect basing his rejection on a single, isolated, statement in the reference. The Bachovchin JBC publication generally describes the characterization of peptide prolyl boronic acids and reports that they are potent inhibitors of some proteinases (see Abstract). The passage relied on by the Examiner appears in a section of the reference describing the preparation of N-boc-Ala-boroPro-pinacol peptides. The Bachovchin JBC publication reports that initial analysis of this peptide preparation indicated that the sample was a "50/50 diastereomeric mixture" and that "attempts to resolve the isomers at this point were not successful". The Bachovchin JBC publication also describes the preparation of H-Ala-boroPro-pinacol from the 50/50 diastereomeric mixture. However, the only description of any type of purification of the stereoisomers is found in the paragraph quoted above.

Applicants submit that this is not sufficient to lead to a conclusion that the Bachovchin JBC publication suggests the claimed invention. The Examiner must consider the reference as a whole when evaluating the patentability of the claims:

> A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. Bausch & Lomb, Inc., v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443,230 USPQ 160, Fed. Cir. 1986.

A fair reading of the Bachovchin JBC publication in its entirety does not suggest either a mixture of Ala-boroPro that is in 95% enantiomeric excess, or a method of obtaining a mixture having this enantiomeric purity. One of ordinary skill in the art would see that the portion of the sentence associating the 95% enriched fraction with the L-boroPro isomer was offered as an explanation of the observation reported in the first portion of the sentence. As reproduced above, the sentence begins by stating "[b]ecause the early fraction has more inhibitory power than the

would not be interpreted by the artisan as an unequivocal statement that the fraction was enriched for the L-isomer. Indeed, no support for this statement, *e.g.*, additional discussion or any spectral data, can be found or derived elsewhere from document itself. Without additional data or explanation, one of ordinary skill in the art would not conclude that the purified enantiomeric forms required by the claims were isolated. This interpretation is reinforced by the last sentence in the quoted passage, which emphasizes that the characterization of the isomers is to be reported in a subsequent publication.

In the present Office Action, the Examiner has also raised questions concerning the declaration submitted with the previous response. The Examiner appears to worry that interpretation of the spectral data is uncertain in view of the possible interconversion between *cis* and *trans* forms of the isomers. He in particular appears to question whether a *trans* isomer exists (see, *e.g.*, page 4, where he states: "Particularly unlikely is the possibility of a 'trans' isomer. . ."). He also inquires specifically as to where in the Biochemistry 32:8723 publication (herein, the "Biochemistry publication") a N->B trans-ring structure is described (see page 5, second full-paragraph of the Office Action).

Applicants maintain that the distinctions between the *cis* and *trans* forms of the isomers are clear in the response and declaration. The Biochemistry publication referred to in the Declaration generally describes the separation of L-Pro-L-boroPro and L-Pro-D-boroPro compounds from a diastereomeric *trans* mixture of the two compounds (see, *e.g.*, the Abstract of the Biochemistry publication). This can be seen in Fig. 1, which is labeled (underlining added): "Structure of <u>*trans*</u>-Pro-boroPro showng chiral centers".

The Biochemistry publication also describes a structure corresponding to the *cis*-isomer. The *cis* isomer is described as a cyclic structure in which the N terminal amino group is covalently bonded to the boron atom (see ¶7 of the declaration submitted in the previous response). In the paragraph bridging pages 8727-28 (entitled "Stability of Pro-boroPro Diastereomers"), the Biochemistry publication reports that the isomers degraded over time to an [illegible] which is described as a "cyclic structure in which the N terminal nitrogen atom

[illegible]

The Examiner also appears to question whether the NMR spectrum provided in the declaration is actually from a pure L,L isomer. As is explained in detail in the declaration, the spectral data reported in the Bachovchin JBC publication can be explained by the *trans* isomer eluting in the early running fraction, and the *cis* isomer eluting in the later-running fraction. The declaration also explains how the purified L, L and L,D enantiomeric forms of the *trans* isomer have distinct spectra, which are not present in the data shown in the Bachovchin JBC paper. The declaration further provides a spectrum of the purified L enantiomer and explains how the NMR spectrum of this isomer is distinguishable from the spectral data described in the Bachovchin JBC publication. Notably, the examiner has not questioned the assignments of the NMR spectral signals, nor has he questioned the Applicants' detailed explanation of how diagnostic spectral bands reveal the presence of various isomeric forms of the compound. Even if there were interconversion between, *e.g.*, the *trans* and *cis* isomers, this has not prevented the isomers from being distinguished in the spectral analyses.

Applicants thus maintain that their explanation of the various isomers in relation to the spectral forms demonstrates why the Bachovchin JBC publication does not suggest compounds falling within the claimed mixture, or a method of making this mixture. To the extent the Examiner remains concerned about Applicants' interpretation of the spectral data, he is asked to show specifically where Applicants' interpretation of the spectral data is flawed.

Applicants note that arguments analogous to those made in the pending application resulted in allowance of claims in European patent application 929222300, which corresponds to the European counterpart of the present application.[1] Attached as Exhibit 1 is a copy of an Examination Report dated April 22, 1997 for the European application. The then-pending claims, which are attached as Exhibit 2, were rejected over the Bachovchin JBC publication (referred to as reference "D2" in the Examination Report). Applicants' foreign associate responded in a letter to the European Patent Office dated October 31, 1997 (attached as Exhibit 3) by pointing out that the Bachovchin publication did not describe the purified L-isomer, or a

method of preparing the purified L-isomer. The application was subsequently allowed in a communication mailed September 29, 1999, which is attached as Exhibit 4. Included with Exhibit 4 are the allowed claims, of which claim 12 is drawn to a preparation comprising an inhibitor present with an isomeric purity of about 96-99%.

Applicants further submit that the Examiner is relying on an erroneous legal proposition by relying on the isolated statement in the JBC publication. The Examiner states at page 4 of the Office Action:

> [T]here would still be one remaining fact, which is that the presumption of enablement is conferred upon the *J. Biol. Chem.* paper. If a hypothetical applicant had conducted a series of experiments, and interpreted all of them incorrectly, or if a hypothetical applicant has conducted no experiments at all, but merely renders a groundless assertion, that disclosure is considered to be "enabling", from a legal perspective, once the patent issues. If the presumption of enablement is granted to someone who has never attempted a single experiment, then surely the presumption of enablement should be bestowed upon an article in a respected journal such as the one at issue. If it is really true that the compound isolated in the *J. Biol. Chem.* paper was an N->B covalently bonded *trans*-ring structure, that fact is of little import from a legal perspective.

Applicants are unaware of any support for the proposition that there is a presumption that even an isolated statement in a publication is *per se* enabling merely by appearing in the publication. Applicants request that the Examiner provide authority for his position. To the contrary, Applicants maintain that the proper inquiry into what a reference teaches or suggests is to determine what it teaches or suggests *in its entirety* to one of ordinary skill in the art. When viewed in its entirety, the Bachovchin JBC publication cannot be said to suggest a mixture in which at least 96% of the carbon atoms bearing boron are of the L-configuration.

The Bachovchin JBC publication also fails for at least two additional reasons to render obvious the claimed invention. As argued in the previous response, the methods for purifying stereoisomers described in the reference would not have lead to the claimed mixture. Thus, there would have been no expectation that the methods described in the Bachovchin JBC publication would have resulted in the claimed invention.

[illegible] continuation and divisional applications.

Second, the Bachovchin JBC publication fails because it is not enabling. The Federal Circuit has stated that a reference must be enabling to be used as the basis for an obviousness rejection:

> In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989).

As is discussed above and in Applicants' previous response, the Bachovchin JBC publication does not describe or suggest a method for purifying the stereoisomers which can result in a mixture in which at least 96% of the carbon atoms bearing boron are in the L-configuration. It was only with Applicants' discovery that the peptides can exist as both geometric and optical isomers, and the elucidation of methods of separating these isomers, that the claimed invention is possible.

Accordingly, in view of the comments presented herein, reconsideration and withdrawal of the rejection over the Bachovchin JBC publication is requested.

Claims 25-51 remain rejected as unpatentable over Bachovchin, U.S. Patent No. 4,935,493 ("Bachovchin'493"), or Bachovchin WO89/03223 ("the Bachovchin PCT publication", or Flentke et al. (Proc. Nat. Acad. Sci. (USA) 88:1556, 1991). The rejection is traversed.

Bachovchin '493 does not describe or suggest a preparation containing a mixture of isomers that is at least 96% enriched for the L-isomer of the compound recited in the claims. This reference also fails to suggest any method for separating a mixture of the L- and D- forms that results in a mixture falling within the claimed invention.

Similarly, the Bachovchin PCT publication describes separation of isomers using the same separation system (silica gel columns) as described in the Bachovchin JBC publication publication. The Flentke reference likewise describes compounds prepared in the Bachovchin JBC publication. The comments offered above to demonstrate the non-obviousness of the

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact either of the undersigned at the telephone number provided below.

Enclosed herewith is a petition for an extension of time and Notice of Appeal, along with the appropriate fees. The Commissioner is hereby authorized to charge any additional fees due with this submission, or credit any overpayment, to Deposit Account No. 50-0311, Reference No. 19644-008 (Tufts-8).

Respectfully submitted,

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